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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/576,778	05/23/2000	Martin Schulein	5843.200-US	1722

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/576,778	SCHULEIN ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,63 and 65-81* is/are pending in the application.

4a) Of the above claim(s) *80* is/are withdrawn from consideration.

5)☒ Claim(s) *81* is/are allowed.

6)☒ Claim(s) *62,63,65,66 and 72-79* is/are rejected.

7)☒ Claim(s) *67-71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER APPEAL BUT BEFORE A BOARD DECISION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11-15-04 has been entered.

Claims 62-63, 65-81 filed on 6-22-04 are currently pending and are present for examination. Claims 62-63, 65-79 and 81 are now under consideration. Claim 80 remains withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. However, when claims 62-63, 65-79, 81 directed to a product, become allowable, pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86), claim 80, directed to the process of using the patentable product, will be rejoined by the Examiner.

Applicants' amendments and arguments filed on 11-15-04 (as part of the appeal brief), have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-63, 65-66, 72-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ß 1,4-endoglucanase enzyme with SEQ ID NO:2 or amino acids 1-456 or 1-617 of SEQ ID NO:2 with an optimum temperature of 65 ° C when measured at a pH of 7.5, active at a pH in the range of 4-11, and isolated from *B.licheniformis*, does not reasonably provide enablement for any such enzyme that has 90%, 95% sequence identity with amino acids 1-456 or 1-617 of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 62-63, 65-66, 72-79 are so broad as to encompass any ß 1,4-endoglucanase enzyme that has 90%, 95% sequence identity with amino acids 1-456 or 1-617 of SEQ ID NO:2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of ß 1,4-endoglucanases broadly encompassed by the

claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single ß 1,4-endoglucanase.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any ß 1,4-endoglucanase having 90% or 95% identity to SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting endoglucanase activity; (B) the general tolerance of ß 1,4-endoglucanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any ß 1,4-endoglucanase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including ß 1,4-endoglucanases with an enormous number of amino acid modifications of the ß 1,4-endoglucanase SEQ ID NOS: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of ß 1,4-endoglucanases having the desired characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the above rejection, applicant has traversed and argue that the rejection under 35 U.S.C. §112, first paragraph is not proper and that claims are indeed enabled. Applicant argues that the Office has provided only arguments that the specification does not enable the claimed invention but has not provided any evidence to support its arguments. Examiner respectfully disagrees with such an argument. The Office has provided a scientific reason to support the argument that the claims are not enabled. And that reason is that the specification has not provided specific guidance to make changes in the amino acid sequence of SEQ ID NO:2 such that the modified sequence continues to have the endoglucanase activity. It is well known in the art that making random changes in an enzyme amino acid sequence can indeed change the functional characteristic of said enzyme and may even eliminate the original activity of said enzyme. When the question of specific guidance to make the changes in the amino acid sequence is posed, all that the applicant has for support in the specification is a highly generalized guidance. Applicant points out that the techniques are routine and well known

(Examiner does not question the availability of techniques to those skilled in the art), such as methods to prepare cDNA libraries, PCR, site directed mutagenesis, shuffling etc. Next, applicant indicates that a table defining conservative amino acid substitutions is provided at page 12 and reference to a number of patents on page 14 describing the shuffling methods. Applicant argues that using such methods one of ordinary skill in the art will be able to routinely produce thousands of mutants in a short period of time and further would be able to identify the claimed enzyme. Examiner respectfully disagrees with above arguments. Regarding the availability of techniques to make changes in an amino acid sequence, Examiner indeed has indicated that methods to make changes in an amino acid sequence are well known. However, specific guidance is required to pick and choose only those amino acids in the enzyme sequence that can be modified, as well as guidance regarding the amino acid/s (from among the twenty naturally occurring) that can be used for replacement or substitution. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities (i.e., replacing every one of the 617 amino acids with any one of the twenty other amino acids followed by testing each and every sequence for the activity). Contrary to the applicant's argument that this would be routine, it would clearly constitute undue experimentation. Applicant argues that some experimentation like carrying out a simple process without special equipment and reaction conditions would be necessary and that such experimentation would not be undue. Examiner respectfully disagrees with such an argument. This is because the protein in question is a fairly large protein comprising at least 456 amino acids and up to 617 amino acids. Applicant's argument that for a protein of such size, the experimentation would not be undue is a highly misplaced argument.

Next, applicant refers to Appendix 2 which is nothing but a compilation of BLAST search. Applicant has searched different enzymes and argues that the results show clearly and convincingly that one of ordinary skill in the art would expect that proteins having 90% sequence identity would have the desired function/utility. It is not clear to the Examiner as to what is the point of the Appendix 2 which comprises the sequence comparisons of proteins isolated from their natural sources. All that the Table in Appendix 2 does is indicate the existence of enzymes with similar function from different sources. It does not provide any guidance to those skilled in the art to make any type of amino acid changes in SEQ ID NO:2. It is not at all clear to the Examiner as to how the information in Appendix 2 points to any type of guidance that can be used to make changes in the instantly claimed SEQ ID NO:2.

Next, applicant brings in the reference of Wilson et al. and argues that said reference establishes a clear relationship between sequence similarity and functional similarity. Applicant argues that Wilson et al. found that functional identity is conserved down to approximately 40% amino acid sequence identity and that among proteins that share 50-100% sequence identity, function is conserved in almost all, and therefore, it is not "unpredictable" to make base changes and maintain desired activity/utility as suggested by the Examiner. Applicant further goes on and argues that the Office's arguments are misplaced because the specification on pages 13-14 discloses that one of ordinary skill in the art can readily identify essential amino acids and the active site in SEQ ID NO:2 by methods well known in the art and that while some experimentation may be necessary such experimentation would not be undue. Examiner respectfully disagrees with such arguments as being persuasive to overcome the above rejection. The teachings of Wilson et al. reference does little or nothing at all in answering the Examiner's

question of specific guidance to make amino acid changes in SEQ ID NO:2. First of all the Wilson et al. reference is a highly generalized reference and is not devoted specifically to endoglucanases. Furthermore, the reference has laid down conditions for the proteins to be similar which the applicant has conveniently ignored. For example, the reference clearly teaches that for pairs of domains that share the same fold, precise function appears to be conserved to ~40% sequence identity, whereas broad functional class is conserved to ~25%. Thus, it is clear to those skilled in the art that information on how the protein folds is required in order to accept Wilson et al.'s conclusion. Without the three dimensional information on protein folding, the teachings of Wilson et al. cannot be applied to any protein. In the instant case, applicant has not provided any information regarding the sequences in SEQ ID NO:2 that are involved in folding and their resistance to change.

In conclusion, Examiner reiterates that the specification fails to provide specific guidance to make amino acid changes in SEQ ID NO:2 and without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities (i.e., replacing every one of the 617 amino acids with any one of the twenty other amino acids followed by testing each and every sequence for the activity). Furthermore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting endoglucanase activity; (B) the general tolerance of ß 1,4-endoglucanase to modification and extent of such tolerance; (C) a

rational and predictable scheme for modifying any ß 1,4-endoglucanase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained.

Examiner has withdrawn the previous rejection of claims rejected under 35 U.S.C. 102(b) as being anticipated by Dhillon et al. (Biotechnol. Lett, Vol. 7(9):695-697, 1985). In view of the applicants response and amendment. Applicants have clearly pointed out that the optimum temperature of the reference enzyme is 55 °C as opposed to the claimed optimum temperature of 65 ° C thereby showing that the two enzymes are different.

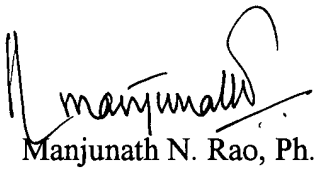
Examiner has also withdrawn the rejection of claim 59 under 35 U.S.C. 103(a) as being unpatentable over Dhillon et al. as applied to claims 43-58, 60-61, and further in view of Olsen et al. (WO 95/26398, 10-5-1995) as applicants have overcome the effects of Dhillon et al. reference.

Conclusion

Claim 81 is allowable.

Claims 67-71 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

June 5, 2006